UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/534,487	03/24/00	REID	L 114231.119

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EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 12/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/534,487	Reid, L.M. et al.
Examiner	**Group Art Unit**
Joseph Woitach	1632

☒ Responsive to communication(s) filed on *Sep 21, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *21-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *21-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants amendment filed August 21, 2000, Paper No. 5, has been entered. Claims 1-20 have been canceled. Claims 21-40 have been added. Claims 21-40 are pending and are under current examination.

This application is a continuation of 09/115,920, which has been allowed, which is a continuation of 08/751,546, now Patent No. 5,789,246, which is a divisional of application 8/165,696, now patent 5,576,207, which is a continuation 7/741,128, now abandoned.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

Claims 2-4, 8-10, 11-13, 14 and 15 rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8 of prior U.S. Patent No. 5,789,246 is withdrawn.

Claims 1, 6, 7, 11-16, 19 and 20 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-9, 17 of copending Application No. 09/115,920 is withdrawn.

Applicants cancellation of claims 1-20, which were product claims drawn to a genetically engineered hepatocyte precursor cell, and adding new method claims drawn to use of said cell, has rendered this rejection moot.

Obvious Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Claims 17 and 18 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 5,789,246 is withdrawn.

Claim 5 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 5,789,246 and claims 1 and 3 of U.S. Patent No. 5,576,207 is withdrawn.

Applicants cancellation of claims 1-20 has rendered this rejection moot.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn. Applicants cancellation of claims 1-20 has rendered this rejection moot.

Claims 21-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.01(a)). The specification is not enabling for the claimed invention because the specification does not provide

sufficient guidance, evidence or exemplification so that an artisan of skill would have been able to make and use the invention as claimed invention without undue experimentation.

In the instant case, claims 21-40 encompass a method of treatment of liver dysfunction in a subject comprising administering a genetically engineered hepatocyte precursor to the subject. As discussed below in detail, the claims encompass a method of *ex vivo* and *in vivo* gene therapy for the treatment of any form of liver dysfunction with a genetically modified hepatocyte precursor cell. Specifically, dependent claims recite that administration of said cells may be through injecting, transplanting, or grafting said cell into the subject, in particular the spleen (claim 25). Further, dependent claims recite that the gene of interest can be inserted into the genome of the cell or maintained extrachromasomally (claims 31 and 32) and recited a list of diseases for which said methodology could be used (claim 34). Finally, dependent claims recite that the genetically engineered hepatocyte precursor can be obtained through *ex vivo* or *in vivo* genetic modification of the hepatocyte precursor cells (claims 37 and 38).

The specification teaches the isolation of a hepatocyte precursor cell from the liver (entire specification, summarized on page 2; lines 1-5), and that culturing the precursor cells with liver stromal cells and an extracellular matrix one can expand said precursor cell (summarized on page 7; lines 13-18). However, the specification does not provide any substantive examples demonstrating that cells isolated in this manner will maintain a precursor like state or will differentiate into mature hepatocytes *in vitro* or *in vivo*. Further, the specification presents only a description for the potential use of the hepatocyte precursor cells in obtaining a genetically

engineered hepatocyte precursor and does not demonstrate that one can culture and genetically manipulate said cells either *in vitro* or *in vivo*. Finally, the specification recites the potential usefulness of genetically engineered hepatocyte precursor cells for treatment of liver dysfunction, and provides a curt description of methodology for inserting a gene of interest and administering said cell for treatment, wherein treatment is affected by expression of a missing or mutated endogenous gene, expression of antisense polynucleotides to suppress expression of an undesired gene (pages 12-14; starting at line 4). Two points of enablement are at issue; first, the amount of guidance and skill in the art to affect treatment of any liver dysfunction by genetically engineering a hepatocyte precursor cell *in vivo* or *ex vivo*, and second, the ability to use the hepatocyte precursor cells in heterologous and xenotransplantation protocols.

First, the physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two subsequently published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Specifically, with respect

to instant application, there is no specific guidance nor examples on how one would treat any liver dysfunction. For example, the specification provides a general description of how one could treat hypercholesteremia by expressing the LDL gene in said cells, however there is no specific guidance on the type of promoter to use, the level of LDL expression one would need to treat a subject or if these cells would proliferate in a subject, how many cells to transplant. Another example describes the treatment of hepatitis infection by expression of anti-sense polynucleotides, however there is no guidance to what oligonucleotides would generate any treatment, what levels of expression one need to inhibit any function of any aspect of viral pathology, or how expression of a polynucleotide in a transplanted cell would affect any form of treatment in other surrounding cells. Further, the claims encompass genetically engineering the hepatocyte precursor *in vivo* and *ex vivo*. While practice of either method (*in vivo* or *ex vivo*) would be subject to the limitations discussed above, the specification is silent on how one would genetically modify a hepatocyte precursor cell in a subject. The Examiner does not argue that one could not isolate a hepatocyte precursor from a liver, however there is no guidance in the specification nor the art of record on how one would target and insert a gene of interest into said cells to create a genetically modified cell. While the art of record does demonstrate that the virus such as adenovirus can infect hepatocytes when injected into a subject, there is no evidence that these vectors reach or infect the normally quiescent hepatocyte precursor cells. The present specification has not provided any guidance to serve as a nexus between the art recognized obstacles of gene therapy protocols and treatment of any liver dysfunction.

Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a method to isolate hepatocyte precursor cells from the liver, however essentially all of the work required to genetically engineer the cells (*in vivo* and *ex vivo*) with the appropriate gene for a particular liver dysfunction, use of the cells for treatment *in vivo*, and the proper route of administration to affect treatment has been left for others.

Finally, while transplantation of tissues from one individual to another who demonstrates a tolerance due to histocompatibility is generally accepted in the art, the successful transfer of cells and tissues from one species to another continues to pose several technical difficulties due to immunological barriers. The specification is not enabling for the claimed invention because the specification fails to provide any guidance, working example or evidence as to how an artisan of skill would have practiced said transfer without undue experimentation. At the time of the invention Ryan highlighted the major obstacle to xenotransplantation as hyper acute rejection (HAR), which leads rapidly to irreversible organ damage and xenograft loss. At the time no agents in clinical practice could prevent HAR (page 967; first paragraph). Two factors; 1) the presence of natural antibodies to the xenograft and 2) compliment, via both classical and alternative pathways are the main forms of HAR. Ryan summarized that 'if xenotransplantation is to become a clinical reality, a clinically relevant means of inhibiting complement activation is required", and "[o]nce compliment-mediated HAR has been inhibited, the full spectrum of cellular

and antibody-mediated inflammatory and immune responses characteristic of acute and chronic rejection" (page 968; final paragraph). The specification is silent with respect to examples or guidance on how one would overcome these problems generally encountered in xenotransplantation.

With respect to transplantation of hepatocytes, currently, these obstacles have still not been overcome. Porter *et al.* in a summary of the work of Ringden *et al.* report that in an attempt to increase graft vs. tumor effect, for treatment of hepatocellular carcinoma, and reduce graft vs. host disease, bone marrow transplantation was done to create mixed chimerism across HLA barriers (page 2004; middle of first column). However, "initial engraftment was transient" and "intensive immunosuppressive therapy was ineffective in reversing 'rejection'" (following line). While the ideal outcome is the generation of mixed chimerism allowing autologous immune reconstruction to induce tolerance to transplantation of non-self cells or tissues, the "conditions required to permit sustained mixed chimerism will need to be elucidated" (page 2004; middle of column two).

A more recent advance in xenotransplantation is the use of genetically modified cells and particular tissues from pigs. As in other allogenic and xenogeneic transplantations, HAR lead to the destruction of transplanted pig tissue when no other steps are taken. Cozzi *et al.* teach that one way to prevent HAR is through the use of regulators of complement activation (RCAs). It is hypothesized that cells from donors which express RCAs could prevent lysis of the cells subsequent to human compliment activation (page 964; top of middle column and figure 1).

While perfused hDAF transgenic organs were resistant to human compliment activation when perfused with human blood, Cozzi *et al.* it si still necessary to demonstrate that such organs had become resistant when transplanted (page 965; column one). Further, while genetic manipulation will overcome compliment-mediated component of rejection, anti-species antibody remains a potential problem in its ability to cause endothelial activation or lysis (page 965; middle column). In summary, there is a need for alternative sources of cells and tissues for transplantation, however, there are many barriers to transplantation, in particular to xenotransplantations, as outlined above. The specification does not provide any guidance nor example as to how an artisan would have dealt with these limitations or overcome the barriers which exist.

Applicants argue that the Examiner has not 'provide[d] evidence or technical reasoning substantiating' rejection of the claims on the grounds that the specification in not enabling, and that the references used are not prior art. See Applicants amendment, page 6, first full and second paragraph. These arguments have been fully considered but are not found persuasive. First, the references of Ryan, Porter *et al.*, Ringden *et al.* and Cozzi *et al.* provide the evidence and basis of lack of enablement of heterologous and xenotransplantation as discussed *supra*. Secondly, while it is true that the references used were published two to nine years after the effective filing date of the instant application, they are used to demonstrate enablement issues that were well known at the time of filing and continue to be technical hurdles in the field. Examiner has provided these references as the basis of the rejection to demonstrate that the instant specification does not

provide the necessary guidance to overcome the art recognized problems of heterologous and xenotransplantation of cells and tissue.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

New Matter

Claims 22 and 24 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment filed September 21, 2000 (paper number 5) is objected to because it introduces new matter into the claims. The added material which is not supported by the original disclosure is as follows: Claim 22 recites 'with the proviso that xenogeneic administration is excluded' and claim 24 recites 'autologous', however these particular embodiments do not have literal nor figurative support in the specification. The specification teaches hepatocyte precursor cells and proposes the use of said cells for the treatment of inherited or acquired diseases (entire specification, summarized on page 13; lines 11-17). Further, the specification actually teaches away for need of this particular embodiment in the recitation of the 'expanded hepatocyte precursor obtained from one liver may thus be administered therapeutically to a plurality of

patients' and that 'administration of such immature cells may also be less likely to stimulate immune rejection'. The only art made of record which teaches the importance of this specific limitation is Porter *et al.* and Ringden *et al.* provided by the Examiner in the previous office action.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 17 and 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Claims 21-40 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 21-39 are unclear and incomplete because they recite a method of treatment of liver dysfunction, however none of the claims recite steps where treatment is affected, only steps of administration.

Claims 21-40 are vague and unclear in the recitation of 'hepatocyte precursor' because the specification teaches only the isolation of specific hepatocyte precursor cells, and no other type of precursors. Recitation of 'hepatocyte precursor cell(s)' would obviate this rejection.

There is no antecedent basis in claim 21 for 'the precursor cells' recited in claim 38.

Claim 24 is unclear and confusing in the recitation of 'is an autologous injecting, transplanting, or grafting' because it is not clear what is meant by the use of the term autologous with these methods. While the definition of autologous is well known in the art, the specification does not define it in conjunction with these methods. Further it is unclear if autologous is modifying only injecting, or if it modifies transplanting and grafting as well.

Claims 26, 37 and 38 are confusing because the method of treatment of claims 21 and 22 presupposes an isolated genetically engineered hepatocyte precursor cell. Claims 26, 37 and 38 recite method steps which precede the practice of and a hepatocyte precursor which has no antecedent basis in claims 21 or 22 and therefore do not further limit claims 21 or 22. Further, claims 26, 37 and 38 recite incomplete methodology, and lack the necessary steps for modifying and obtaining said genetically engineered precursor cell from a hepatocyte precursor cell.

Claim 28 is unclear in the recitation of 'is capable of differentiating into a hepatocyte' because this is a necessary and defining capability of a hepatocyte precursor cell and this recitation implies that certain hepatocyte precursor cells may not be capable of differentiating into hepatocytes.

Claim 29 is vague and unclear in the recitation of 'expresses at least one gene of interest' because it is not clear to what 'gene' the claim is referring. It is unclear if the claim is referring to a transgene introduced into the genetically engineered hepatocyte precursor cell or to a gene of interest which is an endogenous gene. Further, claims 30-33 are unclear in the recitation of 'the gene of interest' for the same reason. These claims are confusing because all the method claims are drawn to genetically engineered hepatocyte precursor cell; however the specification teaches use of the precursor cell by itself for treatment of liver dysfunction (in part by supplying to a subject hepatocytes which provide an endogenous gene product which a subject needs), and so it is not clear in these claims if the method of treatment is drawn to endogenous genes or genetically engineered transgenes.

Claim 40 is unclear in the recitation of a 'drug delivery system' because a drug encompasses many other compounds other than polypeptides which can not be synthesized by a cell. Further, the specification only teaches the expression of potential therapeutic gene products and not administration of other types of drugs. It is unclear therefore in the drug delivery system recited in this claim if other 'drugs' are co-administrated and if so should be recited in the claim, or if 'drug' refers only to a gene product and if so the claim should be drafted to more clearly and specifically define this embodiment.

Claim 40 is vague and unclear in the recitation of 'in a biologically significant amount'. The claim does not recite any specific disease nor conditions for which the system is used, nor a

specific polypeptide which is expressed, therefore one would not know the metes and bounds of what amount or level of expression would be encompassed by this recitation.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached at (703)305-8806.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 306-3076.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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